REACT: Reducing anaesthetic complications in children undergoing tonsillectomies

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## Contents

Background ...................................................................................................... 1  
Aims and Significance ...................................................................................... 2  
Hypothesis ....................................................................................................... 2  
Ethical Issues ................................................................................................... 2  
Methods ........................................................................................................... 3  
  
  Study Population ........................................................................................... 3  
  Inclusion criteria ............................................................................................ 3  
  Exclusion criteria ........................................................................................... 3  
  Study protocol ................................................................................................ 4  
  Study Design .................................................................................................. 4  
Study Team ...................................................................................................... 6  
Data management ........................................................................................... 6  
Adverse Events ............................................................................................... 6  
Replacement of Participant ............................................................................. 7  
Recording of Data ........................................................................................... 7  
Source of Funding ........................................................................................... 7  
Timing .............................................................................................................. 7  
Study Drug Management ............................................................................... 7  
Safety aspects .................................................................................................. 7  
References ....................................................................................................... 8

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Background
Despite being a common procedure, tonsillectomy is still associated with significant morbidity and mortality, particularly in children, in whom hypoxic events are more common.\(^1\) The incidence of fatal respiratory events following tonsillectomy in children is twice that of adults and these events occur more frequently in younger children and those with co-morbid conditions.\(^2\) Moreover, respiratory complications are more common in children with obstructive sleep apnoea and the rate of complications is inversely proportional to age.

An observational study with more than 9000 children, performed by our research team at Princess Margaret Hospital has identified an increased risk for perioperative respiratory adverse events (PRAE) associated with the presence of risk factors in the medical (family) history. Furthermore, it identified Ear, Nose and Throat (ENT) surgery as a stand-alone additional risk factor with tonsillectomy being one of the most incident prone surgeries within this subgroup.\(^3\) Based on past studies at our institution, children undergoing tonsillectomies have on average just over 3 risk factors for PRAE in their medical (family) history and over two thirds suffer from obstructive sleep apnea.\(^3\) In a recently completed randomised control trial by our group looking at the timing of the removal of the laryngeal mask airway in children undergoing tonsillectomies (+/- adenoidectomy) (n=290) we found the incidence of PRAE to be 48.2%. Age is also an independent risk factor for PRAE. With every year of age, the risk for PRAE reduces by 11%.\(^3\)

In order to improve the outcome of these high risk children, we are aiming at developing optimised anaesthetic management strategies. One of those prevention strategies consists of a premedication with inhaled salbutamol prior to surgery. An observational trial in children undergoing elective surgery with a recent upper respiratory tract infection showed, that inhaled salbutamol reduces the incidence of perioperative bronchospasm (5% vs. 11%, p=0.027) and persistent coughing (5.5% vs. 11.5%, p=0.0314) in the perioperative period\(^4\).

We therefore propose a double blinded randomised placebo controlled trial to verify the efficacy of a premedication with inhaled salbutamol in young children (0-8 years) undergoing tonsillectomy (+/- adenoidectomy, +/- grommets) to reduce the incidence of PRAE. Monitoring and recording of PRAE (laryngospasm, bronchospasm, severe and persistent coughing, airway obstruction, oxygen desaturation (<95%) and postoperative stridor) will occur throughout the procedure and in the post anaesthesia care unit (PACU). We hypothesise that children receiving a premedication of inhaled salbutamol will experience significantly less PRAE when compared with children who received placebo preoperatively.
Aims and Significance

Despite the development of anaesthesia management guidelines, PRAE remain a major cause of morbidity and mortality during paediatric anaesthesia, accounting for more than three quarters of critical incidents and nearly one third of all perioperative cardiac arrests.\(^5\)

It is known that the rate of PRAE is approximately 2-folds higher in children undergoing tonsillectomy procedures compared to adults and that the rate of complications is also inversely proportional to age\(^6\). Younger children are at a higher risk for PRAE compared with older children with a decrease in PRAE of 11% with each yearly increase in age.

In recent studies and audits in our institution looking at children undergoing tonsillectomies, we found that approximately half the patients suffer from PRAE. Such a high rate of complications inevitably generates a cascade of linked events such as delays in theatre, with the potential for cancellation of other children due to the lack of theatre time and consecutive increases in waitlist time, unplanned hospital admissions, prolonged hospital stay and additional treatment. Even though most PRAE are not associated with long-term sequelae, it also creates more stress for the child and parents. Furthermore, data from closed malpractice claims in the United States of America (USA) show that nearly half of all claims were due to PRAE with higher incidents of death and brain damage as well as higher compensation payments in children as compared with adults\(^7\).

The development of preventative strategies, incorporated into an optimised anaesthesia management, would help reduce the occurrence of PRAE and address the previously cited issues. Salbutamol is a commonly used drug in the treatment of asthma which is available as an over the counter medication in Australia. A previous observational trial showed that premedication with inhaled salbutamol reduced the incidence of respiratory adverse events and in particular reduced bronchospasm and persistent cough by up to 50% in children with a recent upper respiratory tract infection.\(^4\) This current study aims to test the efficacy of inhaled salbutamol to prevent PRAE in young children undergoing tonsillectomies, who are at a particularly high risk for PRAE in a randomised controlled setting. The secondary objectives are to reduce the delays in theatre and the time spent in PACU due to PRAE, the number of unplanned admissions, prolonged hospital stays and delays in the waiting lists due to sequelae following PRAE.

Hypothesis

We hypothesise that, in children undergoing tonsillectomy (+/- adenoidectomy, +/- grommets) procedures, the incidence of overall PRAE will be significantly reduced by the preoperative treatment with inhaled salbutamol as compared with placebo.

Ethical Issues

Approval from the Princess Margaret Hospital for Children Ethics Committee will be sought prior to any research or clinical investigations being undertaken.
All documents used for the research will be approved by the ethics committee. All children and their families will be informed of the possibility of being approached for research prior to their arrival to the hospital. Written consent consisting of parental/guardian permission will be obtained and great care will be taken to maintain the highest standards regarding consent for clinical research in paediatric anaesthesia. Child consent is impractical within some of the age groups defined but where practical and appropriate child assent will be obtained in conjunction with parental consent. Following the oral information session by our study team, the parents and the child (if applicable) will be handed the information sheets for reading. It will be explained to all families that participation is voluntary and that they can withdraw their participation at any stage without having to justify the reasons for doing so. The withdrawal of participation will not prejudice current or future medical treatment. After sufficient time to read and consider the participation of their child in the study protocol, the study team member performing the consent, will answer all remaining questions. If the parents and child are happy to proceed with their participation in the study, the parent(s) and child (if applicable) and the investigator will sign the consent form. The original consent form will be filed in the study source data file, the parent and child will be given a copy and documentation within the patients notes concerning the type of study the patient is enrolled in will occur.

Methods

Study Population
We will study 484 children, aged 0-8 years, undergoing general anaesthesia for elective tonsillectomy (+/- adenoidectomy, +/- grommets).
There will be two patient groups for the study:
Group one: Children 0-6 years old receiving an endotracheal tube (ETT)
Group two: Children 3-8 years old receiving a Laryngeal mask airway (LMA)

Inclusion criteria
- Children undergoing elective surgery under general anaesthetic
- Male or female aged between 0 and 8 years

Exclusion criteria
- Children receiving a sedating premedication (e.g. midazolam, clonidine) before surgery.
- Children with a known difficult airway or thoracic malformation.
- Children with a known cardiopulmonary disease:
  - Uncorrected congenital heart disease
  - Primary/secondary pulmonary hypertension
  - Cardiac/thoracic malformations/tumours
  - Structural lung changes
The above list is a non-exhaustive list. Any other less common cardiopulmonary conditions will be assessed by the anaesthetist in charge and accounted for in the exclusion criteria list.
Study protocol
The treating anaesthetist’s approval will be sought prior to approaching families of children that may be eligible for recruitment. Once approval is obtained, a member of the research team will proceed with the recruitment procedure. Voluntary written informed consent from the parent/guardian and verbal (and written if appropriate) assent from the children will be obtained prior to any study procedures commencing.

Primary endpoint
The primary endpoint of the study is the occurrence of Perioperative respiratory adverse events (PRAE) in children undergoing tonsillectomy receiving either a premedication of inhaled salbutamol or placebo.

Study Design
Single centre, double blinded, randomised, placebo controlled trial.

Randomisation Procedure
The patients will be randomised by computer generated block randomisation. Following written informed consent, the participant will be assigned the next available participant number. The drug randomisation will be performed by pharmacy at PMH. The patient will receive the study drug corresponding with his/her participant number. The participant number will be used to identify the patient for the duration of the study.
All staff involved with the care of the patient and the data recording and data entering will be blinded to the group allocation.
If un-blinding is necessary for clinical reasons, there will be a sealed randomisation list under key lock in the main theatre complex to allow for immediate access. If the seal needs to be broken for un-blinding, the data safety monitoring committee will be notified immediately.

Study Plan
All participants will be recruited at the pre-anaesthetic visit and randomised to receive either an inhaled placebo (propellant only) or inhaled salbutamol (200 μg; Ventolin, GSK) via a Metered Dose Inhaler (pMDI) and spacer. Each child will receive 2 metered puffs 15-30 min prior to the induction of general anaesthesia. The PMH Nursing practice guidelines section 7.1.2 will be followed for the administration of the placebo/salbutamol to the participants.
The attending anaesthetists, the surgeon, recovery staff, as well as the research staff undertaking lung function assessments will be blinded to the group allocation.

Anaesthesia
Anaesthesia induction will be performed as deemed appropriate by the attending consultant anaesthetist, with either an inhalational induction with sevoflurane or an intravenous induction with propofol. Maintenance of anaesthesia will be performed with sevoflurane. The choice and dose of
analgesia, will be at the discretion of the individual anaesthetist to be able to adjust the analgesia to the individual patient’s needs.

Postoperative Care
All patients will be transported in the lateral position to the postanaesthesia care unit (PACU), after confirmation that the child is able to maintain adequate air exchange. Oxygen saturation will be measured continuously until the patient is discharged from the PACU. Oxygen saturations will be recorded when the patient is calm, and when the pulse oximeter shows consistent detection. Lowest measured \( \text{SpO}_2 \) values will be recorded 10 min before removal of the airway device and at 1, 2, 3, 5, 7, 10, 15, 20, 25, and 30 minutes after removal of the airway device. Any respiratory adverse events (laryngospasm, bronchospasm, desaturation <95%, airway obstruction, severe coughing and/or postoperative stridor), as well as any potential interventions, will be recorded. All children, or their parents, will be interviewed on the ward or at home (via telephone) 1-3 days following the procedure regarding the presence or absence of sore throat, a hoarse voice and/or other respiratory complications.

Respiratory Adverse Events
All PRAE, (i.e. laryngospasm, bronchospasm, oxygen desaturation [<95%], coughing, airway obstruction), will be recorded by an independent blinded observer.

Other parameters assessed
We will assess the time of anaesthesia, the time in PACU, the time on SDPU as well as the number of unplanned hospital admissions (including ICU admissions) for all patients and use this as a basis to calculate actual savings.

Sample Size Calculation and statistics
Sample size calculation
The primary aim of this study is to investigate the difference in prevalence of PRAE between the intervention (salbutamol) and control (placebo) groups. This project will investigate the effects of salbutamol on PRAE, separately for the two different airway devices commonly used, an ETT will be used for 0-6 year old children and an LMA will be used for 3-8 year old children. In our recently completed randomised controlled trial involving tonsillectomy, the prevalence of PRAE was 48.2%. We aim to reduce the prevalence to 24.1% ± 5%. We conservatively selected the upper limit of prevalence of 29.1% (24.1%+5%) for our power and sample size calculation. For the ETT group (for 0-6 year old children), we need 110 children for the intervention and the control groups, respectively, to detect a decreased prevalence of PRAE by 19% (48.2%-29.1%), with a power of 0.8 and at the significance of 0.05. Likewise for our study purpose in the LMA group (for 3-8 year old children), we need the same number of children (n=110) in the intervention and control groups, respectively. Therefore we require 440 children to take part in this project. Furthermore, based on our previous experience, approximately 10%
of the data will not be usable due to changes in clinical requirements for the particular patients or due to patient withdrawal and we thus have to add 10% to our sample size calculation to keep the study appropriately powered. We will therefore recruit 484 patients.

**Statistical analysis**
This is a two-arm clinical trial. Intention to treat strategies will be employed for the analysis. The PRAE outcome of the data collected will be binary. Thus, Chi-square tests will be employed to compare the difference in prevalence of PRAE between the intervention and control groups for children undergoing a tonsillectomy procedure. Binary logistic regression will further be used to assess the effect of salbutamol on PRAE with potential confounding factor variables included in the model. The statistical analysis will be conducted in the two groups (LMA and ETT), respectively. The level of significance used will be 0.05. These statistical analyses will be performed in SPSS environment with the guidance of A/Prof Guicheng Zhang.

**Study Team**
**Principal Investigators**
Prof Britta von Ungern-Sternberg, Chair of Paediatric Anaesthesia, PMH
Prof Graham Hall, Respiratory Physiologist, Telethon Kids Institute and PMH
A/Prof Guicheng Zhang, Biostatistician, PMH and Curtin University

**Associate Investigators**
Dr Anoop Ramgolam, Research Officer, Telethon Kids Institute
Lliana Slevin, Clinical Trial Coordinator, Telethon Kids Institute
Debbie Cooper, Research Assistant, Telethon Kids Institute Research
Lara Oversby, Anaesthetic Research Nurse, PMH

**Data and Safety Monitoring Committee**
Dr. Alison Carlyle, Consultant Anaesthetist, PMH
A/Prof Anthony Kicic, Scientist at Department of Respiratory Medicine, PMH
Dr Julie Marsh, Biostatistician at Telethon Kids Institute

**Data management**
Data management and data entry will be completed by Lara Oversby, Lliana Slevin and Debbie Cooper in the anaesthetic research office. All data will be kept in a password protected database. All study relevant paperwork will be kept under key lock.

**Adverse Events**
It is the responsibility of the Principal investigators to ensure that all adverse events are documented and accurately reported. However, it has to be kept in mind that the study drug salbutamol has an extremely good safety record over decades and is used numerous times every day in theatres at PMH as well as in many institutions worldwide. Salbutamol is available as an over the counter medication in Australia.
Replacement of Participant
Participants who withdraw from the study will not be replaced.

Recording of Data
The data will be entered into a password-protected database on the hospital W-drive and will be deidentified with study identification number only. The original data collection sheet will have patient details and study identification number and will accordingly provide a data trail. Data collection sheets will be stored for 15 years, in a locked cupboard, with access for the research team only. The research team are appropriately credentialled personnel and are bound by Child and Adolescent Health Service (CAHS) confidentiality clauses.

Source of Funding
The Chief investigators and the associative investigators will be performing this study in their non clinical time as well as their spare time. Further funding has been requested/will be requested from varying agencies including SHRAC, and Telethon and Perth Children’s Hospital Grant. Back-up funding is available from research funds from the chief investigators.

Timing
The study will be started following approval by the Ethics Committee. Data collection is expected to take 36 months.

Study Drug Management
The pharmacy at PMH will be responsible for obtaining, blinding and managing the stock of salbutamol and placebo inhalers. They will maintain accountability logs for all stock. The pharmacy will then dispense small batches of inhalers to the anaesthetic research team who will complete full accountability documentation for the stock. The pharmacy accountability logs are checked and signed by both the pharmacist and the research team on receipt and return of all medication. The accountability by the research team includes documentation of stock and expiry dates on the research board in the research office, documentation of expiry on a monthly stock check log, documentation of expiry date and inhaler details on a dispensing log and also on an administration sticker. All of research team will receive training on the management and administration of the study medication prior to working on the study.

Safety aspects
To ensure the safety of randomised patients the following safety parameters and stopping rules have been set. The trial will cease if one of the following criteria are met and if the cause of these criteria has been determined by the Data and Safety Monitoring Committee to be entirely or partly related to the study intervention (salbutamol or placebo):

- Twenty participants per arm of the trial that experience a laryngospasm greater than 2 min and requiring treatment with suxamethonium
- Twenty participants per arm of the trial experience bronchospasm that does not respond to inhaled adrenaline administered after five minutes,
- Ten participants per arm of the trial that have an unplanned intensive care unit admission
Ten participants per arm of the trial experience an allergic reaction as determined by the treating Anaesthetist.

An independent member of the Anaesthetic Department (Dr Alison Carlyle) who is not involved in the trial will receive a study serious adverse event form if any of the above or other serious unexpected events occur during the trial.

The Data and Safety Monitoring Committee will also receive a weekly email to report on all adverse events to monitor for safety parameters and trial conduct on a continuous basis. Ethics will also receive a letter and an adverse event form if any of the before mentioned, or other serious unexpected events occur during the trial.

Participants that experience an adverse event will be followed up in the recovery or intensive care unit and prior to discharge from the hospital by the treating Consultant Anaesthetist and the Chief Investigator or Safety Monitoring Delegate directly after the adverse event.

References

4. von Ungern-Sternberg BS1, Habre W, Erb TO, Heaney M. Salbutamol premedication in children with a recent respiratory tract infection. Paediatr Anaesth. 2009; 19(11);1064-9